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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,764	FIRST, ERIC R.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,13-15,19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,13-15,19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 5-6, 13-15, 19 and 21 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action (second non-final action).

Rejections Withdrawn

1. ***Claim Rejections - 35 USC § 112*** Claim 13 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is herein withdrawn in light of Applicant's traversal and disclosure of additional embodiments not previously appreciated.

Response to Arguments

2. Applicant's arguments filed December 3, 2007 have been fully considered but they are not persuasive.

3. ***Maintained, Claim Rejections - 35 USC § 102*** The rejection of claims 1, 5- 6 , 15, 19 and 21 under 35 U.S.C. 102(e) as being anticipated by Dake et al (US PG-Pub 2005/0196414, effective filing date March 3, 2004) is traversed on the grounds that Dake et al is directed to treatment of muscle spasms and dystonic contractions, and amount administered is sufficient cause muscular paralysis.

4. It is the position of the examiner that Dake et al disclose the instantly claimed invention that includes within its' scope the treatment of anal fissures, a type of pressure sore.

The abstract of Dake et al states: The invention also relates to methods for reducing muscle paralysis and other conditions that may be treated with a botulinum toxin, (abstract); therefore the invention of Dake et al includes other embodiments.

At paragraph [0012] Dake et al discloses the invention to include treatment of anal fissures and further describes this treatment to include "[0013] Topical application of botulinum toxin would provide for a safer and more desirable treatment alternative due to the painless nature of application, the larger treatment surface area that can be covered, the ability to formulate a pure toxin with higher specific activity, the reduced training necessary for applying the botulinum therapeutic, the smaller doses that would be necessary to produce the desired effect, and the lack of a requirement for large wells of toxin to reach a therapeutic clinical result. An effective means for transdermal delivery of botulinum toxin, as well as an effective means for administering botulinum toxin to treat or prevent a number of conditions that does not require injection is thus highly desirable. "

Dake et al describes means for administering smaller doses of botulinum toxin that will produce the desired dermatological effect, where the compositions comprise [0047] …a carrier, vehicle or medium that is compatible with the tissues to which they will be applied.) The term "dermatologically or pharmaceutically acceptable," as used herein, means that the compositions or components thereof so described are suitable for use in contact with these tissues or for use in patients in general without undue toxicity, incompatibility, instability, allergic response, and the like. As appropriate, compositions of the invention may comprise any ingredient conventionally used in the fields under consideration, and particularly in cosmetics and dermatology. The

compositions also may include a quantity of a small anion, preferably a polyvalent anion, for example, phosphate, aspartate, or citrate."

The dosage per treatment encompasses the dosage claimed by Applicant, which would be an amount with the claimed functional characteristic of being an amount that will not paralyze a muscle : [0058] Most preferably, the compositions are administered by or under the direction of a physician or other health care professional. They may be administered in a single treatment or in a series of periodic treatments over time. **For transdermal delivery** of botulinum toxin for the purposes mentioned above, a composition as described above is applied topically to the skin at a location or locations where the effect is desired. In embodiments were an aqueous botulinum toxin/carrier solution is applied directly to the skin, it is preferable to cover the treated area (e.g., with Cetaphil.RTM. moisturizer) or occlude the treated area with a barrier (e.g., Telfa), in order to prevent the solution from drying out, which would lead to a decrease in toxin activity. Because of its nature, most preferably the amount of botulinum toxin applied should be applied with care, at an application rate and frequency of application that will produce the desired result without producing any adverse or undesired results. Accordingly, for instance, topical compositions of the invention should be applied **at a rate of from about 1U to about 20,000U,** preferably from about 1U to about 10,000U botulinum toxin per cm.sup.2 of skin surface. Higher dosages within these ranges could preferably be employed in conjunction with controlled release materials, for instance, or allowed a shorter dwell time on the skin prior to removal.

With respect to Dake et al's claims, claims 51, 54, 71, 126 and 141 all depend from claim 51 directly or indirectly and administer botulinum toxin topically to the skin of a subject,

specifically to the buttocks of the subject to improve wound healing and reduce symptoms associated with injured muscles. The claims are provided here for Applicant's convenience:

51. A method of administering a botulinum toxin to a subject comprising **topically** applying to the **skin or epithelium of the subject** the botulinum toxin in conjunction with an effective amount of a carrier comprising a polymeric backbone having attached positively charged branching groups, wherein the association between the carrier and the botulinum toxin is non-covalent.

54. A method according to claim **51** in which the botulinum toxin is administered to achieve a **desired biologic effect**.

71. A method according to claim **51** in which the botulinum toxin is applied **topically** to the buttocks of the subject or to a portion thereof.

126. A method according to claim **54** in which the botulinum toxin is applied topically for **improvement of wound healing**.

141. A method according to claim **54** in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with **injured muscles**.

Brisinda et al (1999) is cited to provide evidence that anal fissures are associated with sphincter pressure, and reduction of the sphincter pressure aids in the healing process (see Brisinda et al, page 65, col. 2 and page 66, col. 1, paragraph 1). Additionally, Brisinda et al teach that anal fissures are a type of ulcer (see page 66, col. 1, paragraph 2, line 3). Other names for pressure sores, include pressure ulcers, bed sores, and decubitus ulcers. Dake et al treating anal fissures that are associated with pressure, and not contractures or dystonic spasms, which treatment is clearly a species within the instantly claimed genus of methods. Applicant's definition includes treatment of anal fissures and buttocks wounds. Therefore Dake et al still anticipate the instantly claimed method as now claimed.

1. The rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Brisinda et al (1999) is traversed on the grounds that anal fissures are related to spasticity and the instant claims require the claimed methods to treating pressure sores unrelated to contractures or spasticity.

2. It is the position of the examiner that in the instant Specification [0051], the treatment of anal fissures is described as an embodiment within the scope of the instantly claimed methods.

3. Upon reconsideration of Brisinda et al, the examiner found the statement that "Spasm of the anal sphincter has been noted in association with anal fissure (see page 65, col. 2, paragraph 2, lines 1-2)", which is a type of hypertonia (see page 65, col. 2, paragraph 2, line 3) , hypertonia being excessive tone of skeletal muscles; increased resistance of muscle to passive stretching; Brisinda et al defines anal fissures to be "a split in the skin" (page 65, col. 2, first line) associated with sphincter pressure (see page 65, col. 2, paragraph 3, sentence 1) and not involuntary constant spasticity of a muscle.

4. Among the patients treated by Brisinda et al were elderly patients, patients with diarrhea, irritable bowel syndrome, diabetes and recurrent fissure after previous surgery (see page 65, col. 2, paragraph 2, bottom of paragraph). None of these patients are described to be spasm or contracture patients by Brisinda et al. Applicant defines patients without spasm or contracture to include patients after surgery or patients that have diabetes.

5. While the reference does describe a subpopulation of patients that evidence anal fissures due to spasm, there are also patients that developed anal fissures due to age and health conditions (diarrhea, irritable bowel syndrome, diabetes and surgery) which need reduction in sphincter pressure in order to permit healing of the anal wound, a type of pressure sore/ulcer.

6. The patients that have anal fissures due to age or health conditions is a patient population treated by Brisinda et al were able to voluntarily increase anal squeeze pressure (see page 66, col. 1, paragraph 5). If the anal muscles were in a spasm, no voluntary squeeze pressure could have been measured above resting pressure, because the muscle would have been in an involuntary muscle spasm. Therefore within the population of patients treated by Brisinda et al is a population of patients with a pressure associated sore of the anal region that requires a reduction in anal pressure to facilitate healing of the dermatological split skin wound/sore/ulcer.

7. Brisinda et al still anticipates the instantly claimed invention as now claimed.

8. ***Maintained, Claim Rejections - 35 USC § 103*** The rejection of claims 1, 5-6, 14-15,19 rejected under 35 U.S.C. 103(a) as being unpatentable over Rebar et al(2003/0021776 A1) in view of Borodic (PG Pub 2002/0187164) and Gassner (US Pat. 6,447,787) is traversed on the ground that "[D]espite the fact that that Rebar generically discloses "toxin molecules" molecules as carriers, the Office opines that a skilled artisan in view of Rebar would be inspired to instead use toxin molecules as an active agent."

9. It is the position of the examiner that the instant Specification teaches embodiments directed to chimeric toxins that include tetanus toxin and derivatives thereof, and chimera of translocation domains of Clostridial (botulinum, tetanus and derivatives thereof) toxins for use in methods for treating pressure sores. See quoted Specification:

10. [0073] "Botulinum toxin" means a botulinum neurotoxin as either pure toxin (i.e. about 150 kDa weight molecule)… or as a complex …..but **includes** recombinantly made, hybrid, modified, and **chimeric botulinum toxins**.

"[0053] Tetanus toxin, **as wells as derivatives** (i.e. with a non-native targeting moiety), fragments, hybrids and **chimeras thereof can also have therapeutic utility**. The tetanus toxin bears many similarities to the botulinum toxins. Thus, both the tetanus toxin and the botulinum toxins are polypeptides made by closely related species of Clostridium (Clostridium tetani and Clostridium botulinum, respectively). Additionally, both the tetanus toxin and the botulinum toxins are **dichain proteins** composed of a light chain (molecular weight about 50 kD) covalently bound by a single disulfide bond to a heavy chain (molecular weight about 100 kD). Hence, the molecular weight of tetanus toxin and of each of the seven botulinum toxins (non-complexed) is about 150 kD. Furthermore, for both the tetanus toxin and the botulinum toxins, the light chain bears the domain which exhibits intracellular biological (protease) activity, while the heavy chain comprises the receptor binding (immunogenic) and **cell membrane translocational domains**."

Therefore, in light of the described embodiments set forth in the instant Specification, the administered botulinum toxin include chimeras of a derivative Clostridial botulinum toxin comprising a Clostridium botulinum or tetanus toxin or derivatives thereof that include a translocation domain/cell binding domain of the toxin. The rejection under 35 USC 103 was set forth because of the scope of the claims described in the instant Specification including chimeras that are hybrid, modified, chimeric botulinum toxins and all three of the applied reference

describe Clostridial toxins that comprise a Clostridium toxins, albeit a perfringines or botulinum toxin, these toxins comprise translocation domain that could serve to translocate the zinc finger domain of Rebar et al. Additionally, the botulinum toxins that could be used with a reasonable expectation of success in the administered composition of Rebar et al was applied against the claims because the botulinum toxins had been used in methods of treating skin, dermal wounds and/or inflammatory conditions.

The molecule of Rebar et al clearly is a hybrid, modified, chimera of a Clostridial toxin that includes the translocation/binding domain of the toxin, and not a naturally occurring isolated and purified clostridium botulinum toxin of serotype A .

The examiner did not apply Rebar et al under 35 USC 102, but under 35 USC 103, based upon Applicant's embodiments and the guidance and teaching in the prior art of functional equivalents for Clostridium toxins that comprise translocation domains, as well as Rebar et al's guidance and teaching of how a translocation domain from a binary (dichain) toxin can serve to facilitate administration of a chimera to treat a pressure sore.

Rebar et al teach: [0275] Toxin molecules also have the ability to transport polypeptides across cell membranes. Often, such molecules are composed of at least two parts (called "*binary toxins*"): a translocation or binding domain or polypeptide and a separate toxin domain or polypeptide. Typically, the *translocation domain or polypeptide binds* to a cellular receptor, and then the toxin is transported into the cell. Several bacterial toxins, including Clostridium perfringens iota toxin, diphtheria toxin (DT), Pseudomonas exotoxin A (PE), pertussis toxin (PT), Bacillus anthracis toxin, and pertussis adenylate cyclase (CYA), have been used in attempts to deliver peptides to the cell cytosol as internal or amino-terminal **fusions** (Arora et al., J. Biol. Chem., 268:3334-3341 (1993); Perelle et al., Infect. Immun., 61:5147-5156 (1993); Stemnark et al., J. Cell Biol. 113:1025-1032 (1991); Donnelly et al., PNAS 90:3530-3534 (1993); Carbonetti et al., Abstr. Annu. Meet. Am. Soc. Microbiol. 95:295 (1995); Sebo et al., Infect. Immun. 63:3851-3857 (1995); Klimpel et al., PNAS U.S.A. 89:10277-10281 (1992); and Novak et al., J. Biol. Chem. 267:17186-17193 1992)..

Specific embodiments described in Rebar et al include the administration of a fusion protein to promote wound healing of pressure sores:

[0310] Wound treatment is another general type of application in which administration of the ZFPs, nucleic acids and compositions disclosed herein find utility. The ZFPs and nucleic acids can be used to treat significant wounds such as ulcers**, pressure sores** and venous ulcers and burns. Examples of such ulcers are those experienced by diabetic patients. An example of the use of **ZFP fusions** to promote wound healing …...

[0276] Such subsequences can be used to translocate ZFPs across a cell membrane. ZFPs can be conveniently fused to or derivatized with such sequences. Typically, the translocation sequence is provided as part of a fusion protein. Optionally, a linker can be used to link the ZFP and the translocation sequence. Any suitable linker can be used, e.g., a peptide linker.

11. Applicant asserts that Borodic does not motivate the skilled artisan to substitute a Botulinum toxin for Clostridium perfringens iota, and a skilled artisan would not view these entirely different species of bacteria as substitutable.

12. It is the position of the examiner that Clostridium botulinum and Clostridium perfringens are clearly different species of bacteria and at no time did the examiner state that these two species of pathogen are equivelant pathogens, but directed discussion toward the bacterial binary, dichain toxins produced by both bacteria that comprise tranlocation domains that can serve in a chimeric fusion protein to deliver the zinc finger protein of Rebar et al into a desired cell to treat a wound/pressure sore.

13. Applicant's claims include the described embodiments set forth in the instant Specification, which include modified, hybrid and/or chimeric fusion proteins of a tetanus or clostridial botulinum toxins or derivatives thereof (see cited paragraphs from instant Specification above).

14. The secondary references were sited (Borodic and Gassner) for teaching the presence of translocation domains associated with Clostridial binary, dichain toxins that are functional equivalents for Clostridium perfringens iota toxin, the functional equivalents being Clostridium botulinum toxins types A and C2.

15. The secondary references were cited to modify the translocation domain used in the method of Rebar, and were discussed as analogous art where the Clostridium botulinum toxins have been taught for topical and/or wound/skin care, and to show that Clostridium perfringens iota toxin, Clostridium botulinum toxin C2 and Clostridium botulinum toxin A are all binary Clostridial toxins that comprise a translocation domain, a cell binding domain and a toxin domain which could be used/substituted into the fusion protein of Rebar for the purpose of delivering a zinc finger protein to an intracellular location through translocation by the translocation domain of a hybrid, modified, chimeric Clostridium toxin, to include botulinum type A to treat a pressure sore with a reasonable expectation of success.

Therefore the examiner's application of Rebar et al against the instant claims is addressing one of the broadest reasonable interpretations within the scope of the instant claims, wherein the claims may administer a botulinum toxin type A that is a modified, hybrid, chimera toxin, and Rebar et al in view of Borodic and Gassner would administer a chimeric zinc finger protein/translocation domain/Clostridial type A toxin hybrid, modified derivative in view of the teachings of Borodic and Gassner for the purpose of delivering the zinc finger protein to a cell associated with wound healing, specifically pressure sore healing. Rebar et al in view of Borodic and Gassner et al still obviate the instantly claimed invention, for reasons of record and responses set forth herein.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Gregory C. Oliver, MD, FACS, ACS Spring Meeting 2002, slide 35.

18. Dr. Oliver discloses a method that comprises the step of:

a. administering BOTOX (30 units), BOTOX being commercially available serotype A botulinum toxin and debriding a chronic fissure wound, specifically an anal fissure. The instant method recites the term "comprising" and the instantly claimed methods steps may be carried out in any order, therefore Dr. Oliver anticipates the instantly claimed invention as now claimed.

Conclusion

a. This is a non-final action.
a. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
March 4, 2008

/Mark Navarro/
Primary Examiner, Art Unit 1645